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Kabuki Syndrome Is Not Caused by a Microdeletion in the DiGeorge/Velocardiofacial Chromosomal Region Within 22q11.2

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Kabuki syndrome (KS) or Niikawa-Kuroki syndrome is a sporadic disorder characterized by postnatal growth retardation, developmental delay, mild to moderate retardation, and a characteristic facial appearance. Cardiovascular defects, clefts of the lip, palate, or both, and musculoskeletal abnormalities occur in about 50% of patients with KS. The cause of this multiple congenital anomaly syndrome is unknown, and investigators have speculated that KS is a contiguous gene-deletion syndrome. Based on the presence of congenital heart defects in patients with KS, it was suggested that this disorder might share a common cause with the 22q11 deletion syndromes. A preliminary study of 2 patients with KS failed to detect a deletion within 22q11. We report the results of fluorescence in situ hybridization with cosmid probes for loci D22S75 (N25) and D22S259 (R32) within the DiGeorge chromosomal region (DGCR) on metaphase spreads from an additional 5 patients, 2 non-Japanese and 3 Japanese, with KS. None of the 5 had deletions at either locus. It is unlikely that KS is caused by a deletion within 22q11.

KEY WORDS: Kabuki syndrome, chromosome 22q11 deletion, fluorescence in situ hybridization

INTRODUCTION

Kabuki syndrome (KS) comprises postnatal growth retardation, mild to moderate retardation, characteristic facial appearance (thick arched eyebrows, long palpebral fissures with everted lateral lower lid, broad nose with depressed nasal tip, widespaced teeth, and protruberant ears), unusual dermatoglyphics, persistent fetal fingertip pads, musculoskeletal anomalies, cardiovascular defects, and cleft lip/palate [Niikawa et al., 1981, 1988; Kuroki et al., 1981]. Congenital heart defects such as ventricular septal defect, atrial septal defect, tetralogy of Fallot, coarctation of the aorta, patent ductus arteriosus, and transposition of the great vessels occur in about one third of KS patients [Ohdo et al., 1985; Niikawa et al., 1988; Hughes and Davis, 1993; Burke and Jones, 1995]. Although most published cases are Japanese with an estimated incidence of 1 in 32,000 in that country, KS may be common outside of Japan as well [Burke and Jones, 1995]. The cause is unknown. Most cases are sporadic, but autosomal dominant and X-linked inheritance have been proposed [Hala et al., 1989]. Results of cytogenetic studies have been unremarkable in all cases, except for 4 patients with abnormalities of the pseudoautosomal region of either the X or Y chromosomes, and a single patient with a maternally inherited paracentric inversion of the short arm of chromosome 4 [Niikawa et al., 1988; Fryns et al., 1994]. The occurrence of congenital heart defects, cleft palate, minor facial anomalies, and mental retardation suggests a microdeletion syndrome. This combination of anomalies is also seen in association with 22q11 deletions, which raises the possibility that KS might be caused by deletion within 22q11. Two patients with coarctation of the aorta and KS did not have evidence of a 22q11 microdeletion [Hughes and Davis, 1993]. Using fluorescence in situ hybridization (FISH) with two probes from the DiGeorge chromosomal region (DGCR) in 5 patients, we present additional evidence that KS is unlikely to be caused by a deletion of 22q11.2.

CLINICAL REPORTS

Patient 1

A 14-year-old Caucasian girl was born to nonconsanguineous parents of German ancestry, age 34 and 36 years, after a 37-week gestation marked by maternal hypertension. Mild developmental delay and hypotonia

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were noted by age 5 months. Seizures developed at age 5 years. Chronic recurrent diarrhea with *Clostridium difficile* infection started at age 9 years.

There was progressive deceleration of linear growth, reaching 5th centile by age 11 years (<3rd centile for midparental height). Head circumference was approximately 50th centile; there was a slight keel-shape to the anterior part of the head. The eyebrows were thick with a mild acute-arch shape; the left lateral eyebrow and upper lid were hypopigmented. The eyelashes were dark, thick, and long, giving an "outline" to the palpebral fissures. The fissures were long and slightly upslanting. The lower eyelids were mildly everted. There *was malar hypo*plasia and a flat maxilla. The nasal root was high, the bridge wide, and the tip bulbous. There was diastema with persistence of primary and absence of maxillary and mandibular secondary incisors. The palate was high. The ears were protrubertant and the antihelix simple. The nipples were close-set (3rd centile). There were no heart murmurs. There was slightly increased extensibility (190°) of elbows and wrists, brachyclinodactyly of the fifth fingers, brachydactyly of the fourth fingers with absent distal interphalangeal creases, and limited flexion at the third through fifth distal interphalangeal joints. Distal finger pads were prominent and conical. The feet were short, with high metatarsal arches and bulbous toes. There was excessive lumbar lordosis but no scoliosis. There were saccadic movements of the eyes. There was generalized hirsutism with low hairlines. There were three hypopigmented linear nevi along the lines of the dermatomes, and three café-au-lait spots on the thorax.

Patient 2

The patient was referred for genetic evaluation at age 8 years because of a coarctation of the aorta (first diagnosed at age 3 weeks, confirmed by cardiac catheterization, and definitively repaired at 11 months) and a submucous cleft palate (diagnosed and repaired at age 2 years). There were scant details regarding pregnancy, family history, and early medical history, as he was adopted at age 10 months from Bogata, Colombia. In addition to the submucous cleft, there was a small subglottic web, tracheomalacia, and pharyngeal muscle problems. There was a history of chronic middle ear infection, necessitating myringotomy tubes. Audiological testing showed a hearing loss in the high-frequency range.

Motor development, when assessed at age 10 months, was quite delayed. However, with stimulation he showed progress, walking alone at 18 months, and completing toilet training at age 3 years. His onset of speech was delayed, but he was speaking in full sentences by age 3 years. He was diagnosed with attention deficit disorder.

Physical examination at age 8 years showed a height at 50th centile, weight at 50th centile, and head circumference at 25th centile. He had bitemporal narrowing, inverted V-shaped eyebrows, epicanthal folds, lateral eversion of the lower eyelids, and long palpebral fissures. Interpupillary distance was at 80th centile. He had a prominent nasal root, a repaired submucous cleft, a bifid uvula, and persistent fetal finger pads of fingers 3–5 bilaterally.

MATERIALS AND METHODS

Patients

Two patients (1 and 2) were evaluated at the Children's Hospital of Philadelphia. The 3 Japanese patients were described previously [Niikawa et al., 1988]. Peripheral blood lymphocyte cultures or lymphoblastoid cell lines established from these patients were used for cytogenetic-molecular studies.

Fluorescence In Situ Hybridization

Metaphase chromosomes were studied by FISH as previously described [Driscoll et al., 1993]. Two cosmid probes, N25 (D22S75) and R32 (D22S259), previously mapped to 22q11.2 and shown to be deleted in most patients with DiGeorge and velocardiofacial syndromes were used in the present study [Driscoll et al., 1993]. Cosmid cos 82, which maps to the distal long arm of 22, and is not deleted in patients with DiGeorge syndrome (DGS) and velocardiofacial syndrome (VCFS), was used as control probe.

RESULTS

All 5 propositi had hybridization signals on both chromosome 22s at loci D22S75 (N25) and D22S259 (R32), in addition to the signal from the control probe. Thus, these 5 patients with KS do not have deletions of the proximal and distal loci within the DGCR.

DISCUSSION

Kabuki syndrome, DiGeorge syndrome (DGS), and velocardiofacial syndrome (VCFS) are all multiple congenital anomaly syndromes. Cardiovascular anomalies, palatal abnormalilities, minor facial anomalies, developmental delay, and mild retardation are common in all three syndromes. These similarities prompted us and others to determine whether these three disorders are causally related. Previous studies have shown that most patients with DGS and VCFS have microdeletions within chromosomal region 22q11.2 [Driscoll et al., 1993; Kelley et al., 1993]. Although 30–55% of patients with KS have congenital heart defects, the spectrum of malformations commonly seen differs from the lesions associated with the 22q11 deletion syndromes [Niikawa et al., 1988; Philip et al., 1992; Hughes and Davis, 1993; Young et al., 1980; Goldberg et al., 1993; Driscoll et al., 1995]. Coarctation of the aorta is observed in 16–25% of patients with KS, whereas it is rarely seen in DGS and VCFS. Conotruncal cardiac malformations such as interrupted aortic arch, truncus arteriosus, and tetralogy of Fallot are the predominant cardiac lesions seen in the 22q11 deletion syndromes [Van Mierop et al., 1986; Driscoll et al., 1995]. The defects commonly seen in KS are associated with abnormal embryonic blood flow, while the conotruncal defects seen in DGS and VCFS presumably result from abnormalities of neural crest cell migration, suggesting that KS does not share a common pathogenesis or etiology with the 22q11 deletion syndromes [Boughman et al., 1987].

Palatal abnormalities, developmental delay, and mental retardation are frequently seen in patients with KS, DGS, and VCFS. However, distinct characteristics which are not commonly seen in association with the 22q11 deletion syndromes include eversion of the lateral lower eyelid, thick arched eyebrows, ptosis, widespaced teeth, unusual dermatoglyphics, and persistent fetal fingertip pads. Although the constellation of findings seen in KS may be seen in DGS and VCFS and are reminiscent of a microdeletion syndrome, the clinical differences suggest that KS is not pathogenetically related to the 22q11 deletion syndromes. In the present study, FISH of metaphase spreads from 5 patients with KS failed to detect a deletion at the proximal (D22S75) and distal (D22S259) loci within the DGCR. These results confirm our clinical suspicion and suggest that KS is a distinct disorder, causally and pathogenetically unrelated to 22q11 deletion syndromes.

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